



4th WHO R&D Blueprint Consultation on Vaccine evaluation in Public Health Emergencies

Executive Summary

On 30-31 October 2017, WHO convened about 30 experts in clinical trials, epidemiology, regulatory and infectious disease modelling to attend a 4th R&D Blueprint consultation on vaccine evaluation in Public Health Emergencies (PHEs).

Since the first meeting in March 2016, the group has been working on a collaborative research preparedness workplan to improve the way we design, conduct and analyze vaccine efficacy studies in PHEs. The Blueprint priority pathogens were used to frame the conversation and illustrate the group's thinking and rationale based on lessons learned from past and current outbreaks.

Working groups are developing :

- (i) a comprehensive methodological discussion paper on vaccine study designs;
- (ii) a decision tree to guide methodology experts during the design of a vaccine trial and promote discussion around key methodological choices;
- (iii) a simulator using realistic outbreak scenarios to assess trials feasibility and;
- (iv) generic annotated protocols for various study designs.

Summary of activities by Working Groups.

The Boston meeting provided the opportunity to all groups to review all materials and tools being developed by each group, before WHO submits those for online public consultation in Q1 2018. In addition, a series of 4 manuscripts have been drafted, reflecting on each group's work, and will be submitted to a peer-reviewed journal in January 2018.

Summary of activities by groups

Group 1 – Guidance on major study designs to be used in PHEs

The Boston meeting provided the opportunity to collectively review the progress on the guidance document on major vaccine study designs to be used in PHEs, before the document goes on public consultation in January 2018. The document is designed to be a comprehensive standing alone with interactive chapters to facilitate navigation.

4 main points were discussed during the session:

- The role of observational studies in the guidance document and was discussed in the context of the Marburg outbreak in Uganda and Kenya and of small outbreaks in general. Experts agreed that randomization remain a key principle for vaccine evaluation in PHEs, but also recognized that observational studies can be used to generate evidence on vaccine efficacy in exceptional circumstances, to be outlined in the document, as well as highlighting the regulatory limitations and challenges associated.
- Although the document focuses on vaccine efficacy, participants agreed that vaccine safety, special target population, and safety procedures should be emphasized in a dedicated section.
- The role of non-inferiority and superiority studies should be better contextualized. Non-inferiority studies are motivated in settings where you have an intervention already influencing an outcome of interest, and where there is motivation that the alternative vaccine will be better in terms of safety, tolerability, cost, convenience. However, it was recognized that the non-inferiority studies may be unfeasible in outbreaks given the scale and may lead to bio-creep.
- The research question of “can you make a valid inference from two different trial design if you can work out the logistics ?” was addressed in an effort to develop a framework for accumulating evidence across outbreaks and/or trials. Having a pre-specified interim analysis plan and blinding of decision-makers of pooling information from both studies are key principles.
- Participants recognized the need to report on both the Intention-To-Treat versus Per-Protocol analysis and estimates, although the definition of each needs to be clarified.



Group 2 – User-Friendly Interactive Decision-Tree

Based on last consultation feedback, the new framework of the decision-tree was presented and endorsed by the experts. The tool was piloted at two research workshops over the summer:

- the WHO consultation on Zika vaccine evaluation in an effort to promote dialogue and facilitate discussion among participants
- a research capacity building workshop in Africa for both trial planning and training purposes.

The tool is now ready to go on online consultation. However, we are waiting for the completion of the Group 1 guidance document to provide a package documentation between the two materials, as the decision-tree is referencing a rationale for each trial design option in the guidance document. In that regard, the decision-tool can be viewed as a tool to navigate through the complex design elements outlined in the guidance document, in a user-friendly way. In addition, a video tutorial and one example on how we can use the tool for Zika vaccine evaluation have been documented to help the user being familiar with the tool.

Group 3 – Simulating vaccine trials

Group 3 has presented several ways on how to use infectious disease models to guide and inform the design of vaccine trials in outbreaks.

Example 1 – an individual-based model has been used to simulate the Zika epidemic in the Americas in order to guide where vaccine trials could be implemented in 2017. To do so, the 2017 cumulative attack rate in a given area informs locally on the endpoints of interest one can expect and may help to determine the sample size needed for a vaccine trial against that particular endpoint.

Example 2 - an individual-based model has been used to simulate the Ebola epidemic in West-Africa in order to explore the number of rings needed given different vaccine efficacies and disease trajectories. This exercise is relevant to a ring vaccination trial as implemented in the Ebola ça Suffit trial.

Example 3 – Field data from a Guinean population exposed to Ebola cases were used to simulate a contact network in an effort to understand how an epidemic could propagate via



an actual contact network to measure the impact of vaccine trials and other interventions based on the geometry of the contact network.

Group 4 – Annotated Generic Protocols

The starting point for that group is the FDA/NIH clinical trial protocol template for Phase 2b and Phase 3. The group has been tailoring the protocol to provide a generic Zika vaccine trial protocol consistent with a Phase 2b/3 multicenter double-blinded placebo-controlled individually-randomized trial, whose primary hypothesis is that vaccinated individuals with the candidate Zika vaccine are protected against Zika illness of any severity.

Major protocol elements were reviewed based on the outcome of the WHO consultation on Zika vaccine evaluation. The Statistical Analysis Plan was discussed and preliminary sample size calculations were done.

Specific topics

a. Accumulating evidence across trials

For the Blueprint priority pathogens, which typically cause regular and small-scale outbreaks, the evaluation of treatments and vaccines is uncertain and we may not accrue sufficient evidence during one single outbreak to reach conclusive results. Also, in the event of a clinical trial, releasing inconclusive results, too soon, may be misleading to decision-makers and affected countries and can have negative impact on outbreak management.

In this regard, a framework for accumulating evidence across outbreaks and/or studies provides an incentive to funders and investigators to conduct research by protecting them from inconclusive results and affected countries from the release of misleading results. Three approaches to combine evidence across outbreaks and/or trials were proposed: pausing a master protocol, blinded merging of data from two (or more) different studies, conducting a meta-analysis of underpowered trials. All approaches require knowledge of heterogeneity (e.g. strains, contact network, control measures) that may exist across studies and/or outbreaks and which may impact sample size and generalizability of results.

Blinded merging of data from two studies can only provide valid inference if the decision to pool data is pre-specified and decided by people who do not know what the results of the



trials are. It was noted that this approach may inflate the Type-I error, because DSMB may have a tendency to toss out studies that may be marginally futile.

b. Vaccine evaluation for Non-Zaire Ebola outbreaks

For Zaire Ebola outbreaks participants welcomed the SAGE statement although it was also recognized that a non-outbreak setting can be used to look at other vaccines and prime-boost approaches using traditional RCTs. It would give chances to look at other vaccines and duration of protection. Ring vaccination as per the SAGE statement could be used if participants become suddenly exposed.

Participants recognized that we cannot assume that the VSV-ZEBOV cross-protects. Therefore, the VSV-ZEBOV can only be considered as a candidate for non-Zaire and Marburg infections. Criteria for selecting vaccines for evaluation, as well as potential for cross-protection, should be evaluated by an independent group of experts. However, a monovalent VSV backbone expressing the strain of the glycoprotein of the relevant virus could be considered for emergency or experimental use as per SAGE recommendations.

The evaluation approach consensus for new candidate vaccines was to use a multi-arm iRCT within rings with one or more vaccines candidates and a placebo arm. That evaluation setting would require single-dose vaccines and would require similar inclusion/exclusion criteria and similar endpoints as well as a plan for accumulating evidence across outbreaks. Finally, immunogenicity data should be collected as part of that evaluation setting. One variation of that trial design would be to stratify rings according to the risk exposure (e.g. contact and contact of contact).



Next Steps

All materials and tools mentioned in this report will go on online public consultation by Q1 2018. In addition, a series of four manuscripts will be submitted to the same identified peer-reviewed journal.

On December 11-12, WHO will engage another group of experts to initiate a similar process for therapeutics evaluation, partly on the basis on the tools being developed for vaccine evaluation.

In Q2 2018, WHO will organize a pathogen-specific consultation on Lassa vaccine and therapeutics where all the material and tools mentioned will be applied and tailored to the specific case of Lassa vaccine evaluation.

In the event of an outbreak of major concern for which vaccine evaluation is prioritized, WHO will consult the vaccine evaluation group of experts at the earliest opportunity to provide guidance on how to best evaluate vaccine candidates.